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ASSOCIATION OF HAND ANOMALIES WITH CONGENITAL HEART LESIONS IN MENTALLY RETARDED, STATE-INSTITUTIONALIZED PATIENTS

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WITH LOVE AND THANKS

to MARCIA

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to MARCIA

INTRODUCTION

It is a well known clinical axiom that the finding of one congenital anomaly should alert the physician to look further for other possible defects. In addition, certain external congenital malformations seem to be associated with specific internal malformations. Illustrating this point are the associations of low set ears with renal anomalies and the single umbilical artery with renal and cardiac anomalies.

Holt and Oram (1960) reported the association of atrial septal defect with deformities of the radial segment of the upper extremity. These findings seemed logical when one recalled the simultaneous embryogenesis of the upper limb and the heart.

Thus, the author proposed to test the hypothesis that patients with hand anomalies would be more apt to have a congenital heart malformation. Furthermore, one would like, if possible, to delineate the associations between specific types of hand abnormalities and particular kinds of congenital cardiac defects to aid the physician in diagnosis.

Many babies born twenty-five years ago with severe congenital heart malformation did not live long enough even to begin school. However, with the recent progress in cardiac surgery, most children with congenital heart disease can be markedly palliated, if not totally corrected, as long as surgery is done before irreversible pulmonary fibrotic

changes have begun.

As many congenital heart defects are not apparent at birth, it would be most useful for the physician examining the newborn if he were to know that an easily visible hand malformation was a signal to evaluate this child carefully at periodic intervals for evidence of congenital heart anomalies so that any disease found might be corrected before pulmonary hypertension makes repair impossible.

REVIEW OF THE LITERATURE

I. Holt-Oram Syndrome

The Holt-Oram syndrome is one in which cardiac and upper extremity anomalies are transmitted together as a specific entity in an autosomal dominant mode of inheritance. The attached pedigree charts and tables detail the specific lesions which have been described in the thirteen pedigrees reported to date by eleven authors. (See Appendix I).

This entity appears to be transmitted as a dominant, in that it is manifested in the heterozygote. The numerous examples of transmission from father to son rule out sex-linkage.

The chromosomes were normal in nineteen of twenty-one individuals whose karyotypes are described in these studies. Massaumi et. al. (1966) found a minor aberration in chromosome sixteen which was identical in two propositi in two different families. This abnormality consisted of a secondary constriction in the short arm of the No. 16 chromosome setting off a bar-like satellite. However, these variants are known to exist in normal populations (German et.al. 1966).

As the tables in Appendix I detail, the cardiac malformations ranged over a wide variety in the fifty-seven individuals who were diagnosed as having a specific defect.

Anomaly	Clinical	Proved
Atrial septal defect	12	23
Ventricular septal defect	5	14
Patent foramen ovale		2
Endocardial cushion defect		1
Pulmonary stenosis (valvular and peripheral)		1
Coarctation of the aorta		1
Patent ductus arteriosus		4
Anomalous right subclavian artery		4
Anomalous left vena cava		3
Transposition of the great vessels	1	
Anomalous coronary circulation		2

By far the most common malformation was atrial septal defect, occurring in 61% (35/57), with ventricular septal defect in 33% (19/57). Atrial and ventricular septal defects were both present in four individuals (7%).

About 58% of those affected with congenital heart disease were females. Females were also much more likely to have developed pulmonary hypertension from their disease (eight females, but only one male).

Arrhythmias ranged from sinus bradycardia with a long P-R interval and nodal escape to markedly bizarre arrhythmias with atrial-ventricular conduction defect. These arrhythmias were often intermittent. The arrhythmias were generally milder in males (usually consisted of increased P-R interval), where they tended to be more unusual and pronounced in the females.

Skeletal anomalies were as minimal as slight hypoplasia of the thumbs to severe malformations of the entire upper extremity. The radial portion of the hand or forearm was

usually the malformed segment. The anomaly tended to be more severe on the left side, in that the left thumb was often absent whereas the right thumb was a fingerlike digit. Again, skeletal involvement, especially in the hands, was more marked in females.

Within the same family pedigree, the cardias and skeletal anomalies of members of the same sex were usually very similar, even though the cardiac and upper extremity anomalies varied markedly within the pedigree. Females were generally more seriously handicapped.

II. Epidemiology of congenital malformations

A. Incidence

There are several problems inherent in using the epidemiological and statistical method to investigate possible etiologies of syndromes or diseases. For example, the same cause can give rise to many different lesions, e.g. maternal rubella early in pregnancy may produce patent ductus arteriosus, ventricular septal defect, or other congenital heart disease. Conversely, different agents often produce the same constellation of malformations, e.g. patent ductus arteriosus produced by maternal rubella infection or transmitted familially.

When compiling statistics about the incidence of congenital anomalies, one must remember that many fetuses with defects will be spontaneously aborted, while others will survive despite serious malformations. Potter (1960) has estimated that at least 20% of all conceptions terminate before reporting of fetal death becomes mandatory and has stated that in the first trimester it is extremely rare to recover a normal fetus.

Despite these difficulties, there seems to be general agreement that world-wide about one child in forty is born with a major malformation that is noted on the hospital record and requires medical attention (Lamy et.al., 1960; Warkany et. al., 1961; Carter, 1963; British Medical Journal, 1965). The Fetal Life Study at Columbia University

has shown that this rate of 2% to 3% is doubled if the observation period is increased to one year (McIntosh et. al., 1954). But even this 5% figure does not include those anomalies which do not necessarily manifest until childhood or adulthood (e.g. cardiac or visceral).

Although the total incidence of all malformations seems to be about the same in various races, the relative frequencies of the individual defects which go to make the total differ greatly among ethnic groups and places. Examples of these markedly increased incidences include polydactyly in Negroes, dislocated hips in Lapps, cleft lip and palate in Japanese, and anencephaly and spina bifida in Ireland, Scotland, and south Wales (Carter, 1963).

Further evidence for variations among the individual anomalies is found in differential sex ratios. At birth there is an increased male sex ratio among babies with malformations when compared to all births (Lamy et. al., 1960). McIntosh et.al. (1954) found that in liveborn infants surviving more than one month the incidence of congenital malformations was markedly greater in males; 8.4% of all liveborn males and 5.5% of liveborn females had congenital anomalies. Furthermore, this increased male sex ratio held for both white and non-white groups; 7.4% of white males, 9.7% of non-white males, 5.2% of white females, and 5.9% of non-white females had congenital abnormalities. Yet, monstrosities, spina bifida, and meningocoeles

predominate in females whereas circulatory, digestive, and urogenital abnormalities are more prevalent in males (Lamy et.al., 1960).

B. Increased risks of death associated with congenital malformations

Universally the presence of a congenital malformation has deleterious effects in being associated with increased spontaneous abortion, prematurity, and mortality. Wallace et. al. (1953) found the incidence of congenital anomalies doubled in prematures (18.2/1000 livebirths) compared to full-term infants (8.3/1000 livebirths). McIntosh et. al. (1954) confirmed that liveborn infants weighing 2500 grams or less had a significantly increased incidence of defect (9.7%) over those weighing more than 2500 grams (6.7%).

Wallace et.al. (1953) in New York City established that the death rate for premature babies with congenital malformations (372/1000 livebirths) was threefold that for all prematures and the mortality rate for full-term infants with congenital anomalies (92/1000 livebirths) was thirteenfold that for all full-term deliveries. Stevenson et.al. (1950) and McIntosh et.al. (1954) have also confirmed these increased risks:

Category		Malformed	
	Total	Number	Percentage
Stillbirths	787	125	15.9%
Babies dying in less than 10 days	638	84	13.2
Babies living	27,599	468	1.7
Totals	29,024	677	2.3%

(Stevenson et.al., 1950)

Category	Total	Malformed Number	Malformed Percentage
Antepartum deaths	81	11	13.6%
Intrapartum deaths	30	7	23.3
Neonatal deaths (within thirty days)	98	29	29.6
Live births (excluding neonatal deaths)	5,530	386	7.0
Totals	5,739	433	7.5%

(McIntosh et.al. 1954)

Most of these demises occur soon after birth. Lamy et.al. (1960) stated that about 50% of all deaths directly due to congenital malformations occur within the first month of life and about 80% happen within the first year. Wallace et.al. (1953) found that neonatal deaths due to congenital anomalies constituted 15% of New York City neonatal death certificates. The neonatal mortality rate of those born with congenital defects was 145/1000 livebirths, an eightfold increase of the citywide mortality rate for all livebirths.

Carter (1963) has noted that in England and Wales since 1900 the infant mortality due to congenital malformations has remained constant at 4 to 6 per thousand, while the total infant mortality fell dramatically during the same period from 130 per thousand to 20 per thousand. Kretchmer (1964) has emphasized that congenital malformations are not only the major cause of death of infants, but remain among the first ten causes of death up to age thirty-five. His table demonstrates that up to age twenty five it is the only category of death always ranking among

the first five in an area such as California where infections are a relatively uncommon cause of death in infancy and childhood.

LEADING CAUSES OF DEATH - CALIFORNIA, 1960*

Age (Yrs.)	1	2	3	4	5
1	Asphyxia Atelectasis 4.5	Malformations 3.5	Prematurity 3.4	Injury at birth 2.8	Influenza Pneumonia 2.6
1-4	Accidents 31.8	Malformations 13.1	Influenza Pneumonia 12.3	Cancer 10.8	Meningitis 3.3
5-14	Accidents 14.6	Cancer 7.5	Malformations 3.9	Influenza Pneumonia 1.7	Benign and Unspecified Neoplasms 1.0
15-24	Accidents 58.6	Cancer 8.8	Suicide 8.0	Homicide 7.0	Malformations 2.6

*Rates are per 100,000 population; for under one year, rates are per 1,000 live births.

(Kretchmer, 1964)

III. Congenital heart malformations

A. Incidence and prevalence

As cardiac defects are not usually manifest at birth and may become apparent as late as adulthood, good estimates of their incidence are difficult to obtain. Furthermore, the method of ascertainment markedly influences the figure obtained for incidence. Retrospective studies based on physicians reporting defects found to a registry usually find a lower figure than that obtained from a prospective study where physicians do physical examinations on each child looking for defects. Furthermore, the longer the follow-up period with reexaminations the more apt is a cardiac malformation to manifest itself in symptoms or signs.

MacMahon, McKeown, and Record (1953) in a retrospective study of 199,418 births in Birmingham, England, using all available clinical records, all autopsies, and the register of stillbirths and deaths found an incidence of 3.2 cases of congenital heart disease per thousand total births and felt that this figure slightly underestimated the true incidence. McKeown and Record (1960) in a prospective series of 56,760 births in Birmingham using birth information extracted from antenatal and birth records, observations on each child made for the next five years by the "health visitor," and death certificates obtained an incidence for cardiac malformations of 4.18 per thousand births. Harris and Steinberg (1954) doing two physical examinations on all 8,716 consecutive newborns in Rochester, Minnesota, (a

white population) found congenital heart lesions in 7.0 per thousand births. McIntosh et.al. (1954) in the Columbia University Fetal Life Study of 5,964 pregnancies seen before the fourth month, resulting in 6,053 infants examined at birth, six months, and one year, or autopsied, obtained an incidence of 5.5 per thousand livebirths and 8.1 per thousand total births. Carlgren (1959) using the Gothenburg, Sweden, maternity hospitals with two physical examinations on each newborn (58,105 newborns) the city's cardiac clinic with seven to sixteen year follow-up, and the city's necropsy results found an incidence of 6.4 per thousand livebirths.

Higgins (1965) estimated the incidence of congenital heart disease in the United States to be about five per thousand births, which means that at least 20,000 babies are born each year with cardiac malformations. The prevalence is usually about two per thousand in a school-age population. Professor Maurice Campbell (1965), drawing on a lifetime's experience in cardiology with a personal series of over one thousand cases and citing the more recent recent studies, stated that cardiac malformations have an incidence of at least six per thousand livebirths and pointed out that they account for about one-fourth of all developmental anomalies, equalling in frequency the major abnormalities of the central nervous system, i.e. anencephaly, hydrocephaly, and spina bifida, all taken together.

Columbia University's Fetal Life Study found the following distribution of cardiac malformations among infants diagnosed as having congenital heart disease in the first year of life:

Cardiovascular system anomaly	Liveborn (33 infants)	Stillborn and neonatal deaths (16 infants)
Tetralogy of Fallot	3	2
Patent ductus arteriosus	6	-
Other malformations of ductus arteriosus	-	2
Coarctation of aorta	1	-
Right-sided aorta	2	1
Other malformations of great vessels	1	9
Malformations of valves:		
Aortic	-	2
Pulmonary	1	1
Septal defects	3	2
Malformations of coronary vessels	1	1
Endocardial fibrosis	2	1
Miscellaneous	-	2
Unclassified congenital heart disease	22	1
Total malformations	42	27

(McIntosh et.al., 1954)

The relative prevalence of specific lesions changes greatly because of the significant early mortality, especially during the first year, in spite of cardiac surgical advances. At birth, ventricular septal defects account for about 20%, patent ductus arteriosus, atrial septal defect, coarctation of the aorta, pulmonary stenosis (generally valvular), tetralogy of Fallot, and transposition of the great vessels each comprise about 10% and aortic stenosis about 5%. The remaining 15% are compsed of much less common

lesions. Transposition of the great vessels has a very high early mortality. Ventricular septal defect and coarctation of the aorta become less prevalent among those surviving past one year. During childhood ventricular septal defect, atrial septal defect, patent ductus arteriosus, and pulmonary valvular stenosis each comprise about 15%, tetralogy of Fallot about 12%, and coarctation of the aorta and aortic stenosis each about 6% (Campbell, 1965).

The sex ratio of children with congenital heart disease has only a slightly increased preponderance of males: 53% (MacMahon et.al., 1953) and 55% (Carlgren, 1959). For individual anomalies, however, the sex ratio does differ appreciably from chance and sometimes there also seems to be a differential mortality:(See next page).

Patent ductus arteriosus is the only condition which is more common in the female sex at birth and remains so throughout life. Coarctation of the aorta shows an equal incidence at birth . Polani (Campbell, 1965) has suggested that the increased mortality in females with coarctation is possibly because coarctation is often associated with Turner's syndrome and the mortality from Turner's syndrome in the neonatal period is known to be high. Pulmonic stenosis has an equal incidence at birth and continues so. Tetralogy of Fallot and transposition of the great vessels are more common in males at birth and show no evidence of a differential mortality after infancy.

Condition	Percentage of Males			
	At birth[1]	Children[2] 0-15 yrs.	Surgical[3] cases	Children, mostly[4] >5, and adults
Patent ductus arteriosus	40	31	29	27
Atrial septal defect	50	40	38	34
Coarctation of aorta	50	65	62	62
Aortic stenosis	55	60	--	70
Pulmonary stenosis	55	--	49	50
Ventricular septal defect	59	50	56	30
Tetralogy of Fallot	61	60	60	59
Transposition of great vessels	73	68	--	--

1 from MacMahon et. al. (1953) and Carlgren (1959) as quoted in Campbell (1965)

2 from Keith et. al. (1958) as quoted in Campbell (1965)
Many of these children were seen soon after birth.

3 Storstein et. al. (1964)
These were cases referred for surgery, primarily children.

4 Campbell (1965)

Campbell (1965) advances an interesting argument to explain the reversal of the male excess in ventricular septal defect. He found that in 180 cases of ventricular septal defect with a larger number of boys at birth, 57% of the boys were still living who were born since 1940, but only 27% of the boys were still alive who were born before 1940. He also noted that boys reversed their left-to-right shunt, became cyanotic, and died at an earlier age than girls did. He suggested this was probably because boys are less willing than girls to limit their activity and feels that this reasoning explains the differential mortality in both ventricular and atrial septal defect.

These suggestions of the prominent British cardiologists, Professors Polani and Campbell, seem to me very reasonable explanations for the differential mortality of coarctations of the aorta and atrial and ventricular septal defects.

B. Evidence for and against genetic factors

1. Combinations of cardiac malformations

What is the evidence for genetic factors contributing to congenital heart disease? We have already seen that while the incidence of congenital malformations is essentially the same in all races and places, the incidence of specific anomalies varies widely.

Even when known constellations of lesions, e.g. tetralogy of Fallot, are excluded, it has been shown that when

a patient has one congenital heart anomaly, he is much more likely to have a second than expected by chance. In Campbell's experience (1965), in an average of all the acyanotic groups, 13% had a second lesion, a twenty-fold increase in the expected probability. These acyanotic groups included known associations such as aortic stenosis or patent ductus arteriosus with coarctation of the aorta, but excluded the anomalies of ventricular septal defect and pulmonary valvular stenosis which are associated in most cyanotic congenital heart disease.

2. Consanguinity

Campbell (1965) found a two-to-three fold increase of first-cousin marriages in his patients with congenital heart disease (1.1% compared to 0.4-0.5% of first-cousin marriage in general population of Britain). This increased consanguinity was highest and probably significant in situs inversus and dextrocardia, which may be determined in an autosomal recessive pattern. In 379 collected cases of situs inversus, 5.3% were the result of first-cousin marriage, an eleven-fold increase over the general population.

Lamy et.al. (1957) calculated the average coefficient of relationship of the parents of the propositi, $C = \Sigma (1/2)^n$, where n equals number of links in an ancestral chain joining the two parents and passing through a common ancestor, and where the summation is over all the different paths connecting

the parents. The average coefficient of relationship was 3.6 times higher in the series with all types of congenital heart disease compared to a randomly selected control group (C = 2.460 for their series of 1188 sibships with a propositus with congenital heart lesion as compared to C=0.6748 for a random control of 660 sibships of propositi without congenital heart malformation, with the two groups matched as regards age of index cases, social and familial background, etc.). When the average coefficient of relationship was calculated for specific kinds of congenital heart lesions, it was again highest in situs inversus (18.170) and dextrocardia (10.420).

These authors further compared the entire group of 1188 sibships with a propositus with congenital cardiac malformation to the subgroup of 28 sibships from consanguineous matings where the index case had congenital heart defect. (1) There was no significant difference in the prevalence of congenital heart disease in a sib of the propositus in these two groups (prevalence was 7.1% in the subgroup of consanguineous matings compared to 2.5% for the entire group). (2) The propositus had another malformation in addition to congenital heart defect in 17.8% of both groups, so consanguinity did not appear to increase the number of malformations possessed by a single individual. (3) A sibling of the propositus had a malformation other than congenital cardiac disease in 10.7% of consanguineous matings as compared to

0.93% of the entire group, a significant difference ($p < 0.05$). (4) Excluding the propositi, the frequency of all individuals exhibiting congenital heart disease or another malformation was 17.8% in consanguineous sibships as compared to 2.7% of all sibships, a difference again significant at the $p < 0.05$ level. Thus these authors concluded that consanguinity increased the frequency of all malformations and only secondarily the frequency of congenital heart malformations.

In summary, then, consanguinity seems to be of importance in situs inversus and dextrocardia, both of which may be determined in an autosomal recessive pattern and where consanguinity would then increase the chance of producing a homozygote who would phenotypically express the defect.

3. Concordance

The concordance for monzygotic twins for a strictly genetic disorder should approximate 100%.

However, the concordance for monozygotic twins for congenital heart disease is low and about the same as concordance for dizygotic twins (Uchida et.al., 1957; Carter, 1963).

4. Risk of recurrence in a family

This risk of recurrence in a sib born after the propositus with congenital heart defect is low, but it is still increased over the general population.

McKeown et.al. (1953) found an incidence of 18/1000 births of congenital heart defects in sibs born after a propositus with congenital cardiac anomaly compared to an incidence of congenital heart lesion of 3.2/1000 births in the general population, a six-fold increase. Campbell (1965) found a 1.7% incidence of congenital heart abnormality in sibs of propositi with congenital cardiac malformation, a three-fold increased chance compared to the general British population (0.6%). These figures were not corrected for family size, but it is well known that parents often limit the size of their family after a child is born with a malformation. Thus one might expect that instead of a large family, which would increase the probability of a second child with defect being born by chance alone, that these were smaller families.

Furthermore, Campbell found the same defect as that of the propositus about 15 to 20 times as often as would be expected; 0.95% of sibs have the same abnormality as opposed to the 0.06% expectation by chance of having the same anomaly (expectation is even less for the more unusual anomalies). Anderson (1954) confirmed the strong tendency in patent ductus arteriosus for the recurrent heart defect to be identical. Wood (1958) in a consecutive series of 1250 patients with congenital cardiac disease found that when congenital heart anomalies occurred in more than one member of a family (which happened in 5% of the cases), it was

nearly always of the same kind. This held true whether the lesion was patent ductus arteriosus, atrial septal defect, ventricular septal defect, coarctation of the aorta, aortic stenosis, pulmonic stenosis, tetralogy of Fallot, or familial cardiomegaly.

There seems to be no increased incidence of congenital heart malformations in parents of children with congenital cardiac lesions (McKeown et.al., 1953 ; Campbell, 1965). However, it must be remembered that before the advent of cardiac surgery, patients with defects such as tranposition of the great vessels never survived long enough to become parents.

5. Parental age

What are the effects of increased parental age in congenital heart disease? The effect of increased maternal age in predisposing to Down's syndrome and the association of Down's syndrome with endocardial cushion defect and septal defects is well known. MacMahon (1952) found that when birth rank was held constant, there was a preponderance in the maternal age group 38-48 for births of infants with congenital cardiac malformation, and this increase was significantly higher than controls. However, when known Down's syndrome patients were excluded (and the ascertainment of patients with Down's syndrome was probably not complete), the difference was reduced considerably and was no longer significant.

Lamy et.al. (1957) found that neither the mean maternal age for the congenital heart anomaly group (28.39 years) was significantly different from the control (28.84 years) nor was the mean paternal age for the congenital cardiac defect group (31.13 years) significantly different from the control (30.80 years). Campbell (1965) found that the mean age of all mothers of children with various types of congenital heart lesions was no greater than would be expected (between 28.47 and 29.35 years) when compared to the general population of Britain. In Ehlers and Engle's study (1966) neither the mean maternal age nor the mean paternal age had any effect on the presence of congenital cardiac disease.

Thus, increased maternal age is important in predisposing to chromosomal non-disjunction and thus to producing a baby with Down's syndrome with trisomy of chromosome 21, which often has endocardial cushion defect with atrial septal defect, secundum type, and ventricular septal defect associated. When children with Down's syndrome are excluded from the total group with congenital heart defect, increased maternal age does not seem to be important in producing children with congenital heart malformation.

Penrose has suggested that instead of just computing the increase in the mean maternal age, it is more useful to calculate the difference between the means of the paternal and maternal ages, since an undue excess of the paternal age

raises the posibility of a "failure to copy genes correctly,"[1] as the male germ line undergoes a much larger number of cell divisions than the female and this suggests mutation during spermatogonial division.

Campbell (1965) pointed out that although neither difference alone was significant, his calculated excess of the mean paternal age over the maternal age in Lamy's study, 2.90 years against 1.94 years in controls, was significant. In Campbell's study, there was an increase of the mean paternal age over mean maternal age in each of the separate groups of heart disease (average 3.27 years) as against the general population (2.74 years). It was least and probably not significant for coarctation of the aorta (6%). But it was at least 17% in all other groups: patent ductus arteriosus (17%), atrial septal defect (17%), tetralogy of Fallot (21%), ventricular septal defect (25%), and pulmonary valvular stenosis (27%). Campbell concludes that these differences in the difference of the mean paternal and maternal ages are "therefore suggestive of a genetic factor"[2] in congenital heart disease.

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1 Penrose, L.S., "Parental Age and Mutation," Lancet, 2, (1955), p. 312.

2 Campbell, Maurice, "Causes of Malformation of the Heart," British Medical Journal, 5, (1965), p. 899.

6. Birth rank

MacMahon (1952), Campbell (1965), and Ehlers et.al. (1966) found that birth order alone has no influence on predisposition to congenital heart disease, but two other studies suggested that increased parity is of some importance in older women. Richards et.al. (1955) found a greater risk of having a child with congenital heart lesions in the third pregnancy as opposed to the first, especially in women over thirty. Lamy et.al. (1957) showed that if maternal age was held constant, birth rank was siginficantly higher for children with congenital heart anomalies in the maternal age groups 25-29 and 30-34.

In patent ductus arteriosus specifically MacMahon (1952) did show that this lesion was much more common in first than later births (51.4% of all patients with patent ductus arteriosus were first born compared to 36.6% firstborn of control series of 1,015 obtained by taking every two-hundredth name from the birth registrars; a significant different of 15.8 $\pm$ 7.6 standard error).

7. Season of birth

MacMahon (1952) in Birmingham and Ehlers et.al. (1966) in this country did not find any relation between congenital heart disease and season of birth. However, season of birth was a factor of definite importance in congenital cardiac malformations during rubella epidemics (Higgins, 1965).

Otherwise, it does not seem to play a role except in patent ductus arteriosus.

In England, two studies have shown a consistently increased seasonal incidence for patent ductus arteriosus for girls (not for boys; they are distributed more equally). Record and McKeown (1953) in Birmingham found the increased rnage from May to December, with a peak in July and August, while Campbell (1965) found the range from May to November with an August peak.

8. Chromosome studies

Chromosomes studies in patients with congenital heart disease have generally shown normal karotypes, although two studies have shown minor variants.

Makino (Grumbach et.al., 1963) studied twenty-two patients with congenital heart disease. Ten of the twenty-two had a partial deletion of No. 16 chromosome so that it was heterologous (four with atrial septal defect, two with both atrial and ventricular septal defect, and four with congenital heart disease of unknown type).

German et.al. (1966) studied chromosomes in thirty-five index patients with congenital cardiac malformation, twenty-nine of their relatives who also had congenital heart anomalies, and twenty-one other relatives without congenital cardiac defect. In four of the thirty-five index cases he found a small chromosomal variant. In each case, this

variant was familial, occurring both in relatives affected and unaffected with congenital heart disease, so that variants were found in a total of eleven of eighty-five karotypes examined. These variants included enlarged short arm of member of group 13-15 in two families, heteromorphic No. 16 in one family, and satellites on No. 17 in one family. German stated that these variants are known to exist in apparently normal populations.

9. Summary

I would have to agree with Lamy that "both genetic and non-genetic factors play a part in the etiology of congenital heart disease. The relative importance of genetic and non-genetic factors appears to vary substantially from one clinical subgroup to another."[3]

The finding that a patient with one heart anomaly is much more likely to have a second cardiac malformation and that there is an increased risk of having a sib with congenital heart defect born after the propositus suggests that genetic factors may be implicated in congenital heart disease. Consanguinity is important in situs inversus and dextrocardia, both of which are thought to be inherited as autosomal recessives.

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3 Lamy, Maurice, de Grouchy, Jean, and Schweisguth, Odile. "Genetic and Non-Genetic Factors in the Epidemiology of Congenital Heart Disease: A study of 1188 cases." American Journal of Human Genetics, 9,(1957), p. 39.

However, concordance for omonzygotic twins is low when all types of congenital heart disease are taken together, whereas it should be 100% in a strictly genetic disease. Chromosome studies of patients with congenital heart malformation usually reveal normal karyotypes. Increased maternal age does not seem to be important except in predisposition to maternal non-disjunction and producing a child with Down's syndrome. Possibly the excess of the mean paternal age over the mean maternal age shown in two studies is significant, but it is difficult to assess just what the operant genetic factor might be (Lamy et.al. 1957; Campbell, 1965).

Environment was certainly of definite importance during rubella epidemics. It seems possible that the importance of first births in patent ductus arteriosus might be because first labors are more prolonged, with greater anoxia, and thus the stimulus for closing of the ductus is not as great.

The term congenital heart disease covers a wide range of complex conditions. The relative importance of genetic and environmental factors varies widely depending on the particular condition, and the causation is probably multi-factorial.

IV. Upper-extremity malformations

A. Incidence

Estimates of the frequency of upper-extremity malformations are most difficult to obtain because the published reports do not usually state whether the various types of dactylism are noted in the hands or feet. Bunnell (1964) reported that the incidence of hand deformities varies from 0.15 to 5.4/1000 livebirths. The following tables from four different studies done in the United States States illustrate the variance in reported frequency.

Anomaly	Surviving Infants	Neonatal Deaths	Stillbirths	Incidence per 1000 livebirths
Clubhands, with or without clubfeet	2	1	0	0.10
Polydactyly	22	0	0	0.75
Missing extremities	8	0	0	0.28
Syndactylism	14	0	0	0.48

(Stevenson et.al. 1950)

Anomaly	Number Reported	Neonatal Deaths	Incidence per 1000 livebirths
Adactylism, polydactylism, and syndactylism	205	10	1.26

(Wallace et.al. 1953)

Anomaly	Liveborn	Neonatal Deaths and Stillbirths	Incidence per 1000 livebirths
Polydactyly of fingers	30	2	5.3
Syndactyly or of toes	11	3	2.3
Flexion deformities	11	0	1.8
Anomaly of digits undiagnosed	0	1	0.2
Gargoylism	1	0	0.2

(McIntosh et.al., 1954)

Anomaly	Total Number	Full Term Male	Full Term Female	Premature Male	Premature Female	Incidence per 1000 livebirths
Polydactyly	4	3	1 (1)			0.4
Polydactyly with syndactyly toes 2 & 3	1	1				0.1
Syndactyly	2	1	1			0.2
Absent phalanges right hand	1	1 (1)				0.1
Absent right 5th finger and bowing of middle phalanx of 2nd finger	1	1				0.1
Absent left thumb	2		1 (1)	1 (1)		0.2
Amelia left hand	1	1				0.1
Micromelia left hand	1		1 (1)			0.1

( ) = infants with major additional anomalies

(Harris et.al. 1954)

B. Genetic

1. Racial differences

Several studies have confirmed that polydactylism is definitely more common in Negroes and that this color difference does not hold for ectrodactylism or syndactylism.

CONDITION	ETHNIC GROUP: Incidence/1000 livebirths				Study
	White	Negro	Japanese	Mulatto	
Ectrodactylia	0.09				Book (1951)
	0.06	0.03			Shapiro (1958)
			0.03		Neel (1958)
	0.13	0.61		0.26	Saldanha (1963)
Syndactylia	0.17	0.06			Shapiro (1958)
Polydactylia	0.68				Book (1951)
	0.58	4.00			Wallace (1953)
	0.5				Harris (1954)
	0.30	2.58			Shapiro (1958)
			0.89		Neel (1958)
	2.45	7.00		5.26	Saldanha (1963)

2. Parental age

Penrose (1960) has shown that in achrondroplasia, acrocephalosyndactyly, and arachnodactyly the average parental age is great; this effect resulted entirely from older paternal age, with maternal age not of importance.

3. Mode of transmission

Bell has shown that in certain families both brachy-

dactyly (1951) and syndactyly (1953) are transmitted as autosomal dominants in that the defects manifest in the heterozygote.

V. Association of hand and heart malformations

A. Incidence

There is general agreement that patients with congenital heart disease have a much increased chance of having a second malformation, which may be of almost any type. Lamy et.al. (1957) and Campbell (1965) in clinical series found that 12% of children with congenital heart disease had a second malformation (a five-fold increase over chance expectation). Higgins (1965) cites six studies done from 1898 to 1955 which obtained incidences of from 11% to 36% of associated malformations of other systems in individuals with cardiovascular malformations, the higher incidences generally being in autopsy populations.

MacMahon et.al. (1953) found that 5.1% of children with congenital heart disease had an associated skeletal malformation.

Wiland (1956) found that 9.5% of the necropsy cases with congenital heart malformation had an associated musculoskeletal anomaly. Although the musculoskeletal anomalies were extremely variable, the most common malformations were of the fingers (polydactyly, absence of digits, and contractures of one or more fingers), occurring in 4% of all children with congenital heart malformations. Furthermore, defects in the interatrial and interventricular septa were associated with the highest incidence of extracardiac anomalies, while abnormalities in the development of the

aortico-pulmonary septum had the lowest incidence of associated malformations (no extracardiac anomalies in transposition of the great vessels and very low incidence in persistent truncus arteriosus).

Lamy et.al. (1957) found that 4.25% of children with congenital heart disease had associated multiple malformations of the hands and upper extremities and 1.42% had syndactyly of hands or feet.

Wood (1958) very briefly noted that in a consecutive series of 1250 cases of congenital heart disease (in which there was no statement that extremity deformities were ascertained) that it was found that seven of eight patients with limb deformities had ventricular septal defect, three of three with polydactyly had tetralogy of Fallot, and that arachnodactyly was far more often associated with atrial septal defect than with any other anomaly (arachnodactyly occurred in 15% of simple atrial septal defect and in 12% of atrial septal defect with pulmonic stenosis and reversed shunt).

Boesen (1963) found a bone and joint malformation prevalence in 16% of his clinical series and in 17% of his autopsy series of patients with congenital cardiac anomalies. He confirmed Wiland's finding that it was very unusual to get extracardiac malformations in patients with complete tranposition of the great vessels. In both clinical and necropsy groups, atrial septal defects were more often

combined with harelip and cleft palate while in ventricular septal defects bone and joint malformations were the most common.

Stevenson et.al. (1950) made a most interesting observation regarding the association of hand and heart anomalies. He used as a basis Arey's table (1946) which showed the development of the various organs according to the embryo's age and then attempted to determine the gestational month in which each defect presumably appeared. The congenitally malformed infants were then reclassified by the system affected and tabulated against the month in which the embryological origin of the defect was presumed to be.

System Affected	Month During Gestation When Defect Developed			
	1	2	3	4
Central nervous	59	32	27	0
Musculoskeletal	0	92	9	0
Cardiovascular	4	55	0	0
Genitourinary	0	2	1	27

(Stevenson et.al. 1950)

Central nervous system defects had their origin throughout all of the first trimester, while cardiovascular and musculoskeletal anomalies were remarkably concentrated during the second month of gestation.

B. Thalidomide lesions

Associated lesions might result from a teratogen acting on the developing hands and heart of the foetus. Both the limb buds and the primitive tube-heart appear in the embryo during the fourth week of foetal life. The differentiating upper limbs and heart and great vessels then complete the major portion of their maturation during the fourth to sixth weeks (Arey, 1965). These could be simultaneously affected by an abnormal factor in their environment acting adversely on their normal evolution.

Support for this suggestion comes from the European and Australian outbreak of phocomelia caused by the drug thalidomide. If thalidomide was ingested by the pregnant mother from the 34th to 50th day after her last menstrual period, there was greater than a 50% risk of having an affected child (Lenz, 1966). Lenz has delineated the specific time of action. (See Table on page 37).

Other anomalies noted included saddle nose; midline facial capillary hemangioma, most commonly on upper lip, nose, and frontal area; gastrointestinal tract: atresia of esophagus, pyloric and duodenal stenosis, malrotation, agenesis of appendix and cecum and imperforate anus; urinary tract: hypoplasia and agenesis of urinary tract and kidney and also horseshoe kidney; genital tract: bicornuate uterus, atresia or absence of vagina, and rectovaginal fistula.

Day of Ingestion	Part Affected
34--38	Anotia or gross abnormalities of ears. Paralysis of cranial nerves III, IV, VI, and VII. Sometimes also duplication of thumbs.
39--44	Amelia or almost complete absence of arms.
< 42	No phocomelia or absence of legs.
44--48	Aplasia of femora or tibiae
> 45	Complete or almost complete absence of legs not observed.
About 50	Triphalangism of thumbs Sometimes stenosis of rectum
40--45	Aplasia of gallbladder Atresia of duodenum Most cardiac anomalies (although some congenital heart disease a few days earlier)

(Lenz, 1963)

Intelligence was thought to be normal. (Mellin, 1962; Lenz 1962, 1963, 1966; Martin, 1964).

It is not known exactly how many foetuses were at risk from maternal thalidomide ingestion or how many foetuses were born deformed. In Australia, McBride (1961) found forty mothers who took thalidomide. Of these, twenty-three had normal babies, but only three of the twenty-three took the drug within the critical time of 35-50 days after the last menstrual period. The remaining seventeen had abnormal babies, with fourteen of these babies exhibiting the typical anomalies

and ten of these malformed infants not surviving.

Lenz (1963) stated that there were in England and Wales 260 living cases of typically malformed infants whose mothers had ingested thalidomide, 85 deceased, and 42 suspected, in Scotland 56 cases, and in the Netherlands 25 cases. Spiers (1963) has suggested that the British and Scottish figures probably represented about 50% of those affected. Lenz (1963) found 78 cases in 17,409 births in thirteen obstetric departments in Western Germany. He noted an abrupt decline in the incidence of phocomelia eight months after the withdrawal from the market of thalidomide; only two cases occurred after this time and both mothers had taken thalidomide. The West German Health Ministry has just reported that thalidomide was responsible for deformities in 2,625 children.[4]

Of children malformed due to maternal thalidomide ingestion, the arms were abnormal in about 80%, affecting preferentially the thumbs and radii, and in almost 20% the ears were absent or severely hypoplastic. In about 65% to 75% only the arms were affected, in nearly 10% to 25% both arms and legs, and in approximately 2% to 5% only legs. When legs were affected, the tibia was most often missing (Mellin, 1962; Lenz, 1963, 1966).

Congenital heart disease seems to be a lesion frequently associated with the abnormal arms. When Taussig investigated the German outbreak of phocomelia in 1962, she stated that in

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[4] A.M.A. News, February 12, 1968, page 2.

Lenz's series of 203, the malformation most commonly associated with anomalous upper extremities (other than abnormal ears), was congenital heart malformations (17/203 = 8.4%). The anomalies included hypoplasia of the aorta, defects of auricular and ventricular septum, all forms of transposition of the great vessels, tetralogy of Fallot, and pulmonary stenosis. In a necropsy series of fourteen cases with maternal thalidomide ingestion, five had tetralogy of Fallot and four had ventricular septal defect (9/14 =64.3%) (Pliess, 1962). Of forty-nine cases in an appendix to a discussion by Lenz on thalidomide, seven had a congenital heart defect (7/49 = 14.3%). One child suspected of congenital heart disease died on the second day of life, one had a patent ductus arteriosus, two had ventricular septal defect and truncus arteriosus communis, and one had undiagnosed congenital heart defect, possibly atrial septal defect of secundum type (Lenz, 1963).

The thalidomide saga, then, is an example of an ingested drug which was harmless to the mother, but in the environment of the foetus was a teratogen acting at a series of specific embryologic stages to produce characteristic patterns of malformation which included both the hands and heart.

SPECIFIC AIMS OF THIS INVESTIGATION

As rapid strides are being made in cardiovascular surgery, many patients who would formerly have died as infants are now surviving to adulthood and bearing children. Thus it becomes even more important to define the mode of inheritance of various types of cardiac anomalies so that rational genetic counseling can be given.

Prior to June, 1965, when this study was started, seven instances of the familial transmission of congenital heart lesions in association with upper-extremity malformations, especially of the digits (Holt-Oram syndrome), had been reported. In these cases, there was wide variation in the types of upper-extremity and cardiovascular anomalies observed, even within the same pedigree.

The Holt-Oram syndrome has been delineated now as one in which upper limb anomalies, affecting primarily the radial segment, and congenital heart lesions, most often atrial and ventricular septal defects, sometimes associated with bizarre arrhythmias, are inherited together as an autosomal dominant trait.

Several other clinical syndromes are known in which congenital heart disease is associated with an upper extremity malformation. These entities include D_1 trisomy of chromosomes 13-15 (polydactyly, ventricular septal defect, and dextroversion or dextrocardia, with atrial septal defect in 1/3); E_1 trisomy of chromosomes 16-18 (archnodactyly,

flexion contracture of fingers, ventricular septal defect, and large patent ductus arteriosus); Down's trisomy of chromosome 21 (short, stubby hands with brachymesophalangia of fifth fingers, endocardial cushion defect with atrial septal defect, secundum type, and ventricular septal defect, either alone or in combination with other lesions); Turner's (short metacarpals, cubitus vulgus, XO/XO type coarctation of aorta, XO/XX type pulmonic stenosis with atrial septal defect); Marfan's (arachnodactyly, aortia media changes leading to diffuse or dissecting aneurysm, aortic incompetence, inherited as autosomal dominant); Fanconi's panmyelopathy (aplasia of radius and thumbs with heart malformations, inherited as autosomal recessive); Ellis and van Crevald syndrome (chondrodystrophic dwarfism, polydactyly, dystrophy of fingernails, single atrium, inherited as autosomal recessive); Laurence-Moon-Biedl syndrome (polydactyly, syndactyly, congenital heart disease inherited as autosomal recessive). (Bell, 1958; Keith et al., 1958; McKusick, 1964; Campbell, 1965; Holmes, 1965; and Rodhe, 1966).

Each of these conditions represents a generalized defect which manifests itself in a varied pattern of malformation. Although neither the upper-extremity abnormality nor the cardiovascular lesion is diagnostic of the syndrome, the associated defects are characteristic of it.

Just as the pediatrician is alerted to a probable

abnormality of the genitourinary system when he notes low-set, malformed ears, so it would be useful if the physician examining the newborn was signaled by an external anomaly of the hand to follow the infant carefully for evidence of congenital heart disease which would not necessarily be manifest at birth. Careful periodic cardiovascular evaluation is particularly important in this era of rapidly advancing cardiac surgery, when the child with congenital heart malformation can often be markedly palliated, if not totally corrected, before irreversible pulmonary hypertension has set in.

One would first thus like to know if simple visual inspection of the hands might be a diagnostic aid in the detection of congenital heart lesions. Since cardiac malformations appear commonly with musculoskeletal anomalies (in which system the most common malformations are those of the fingers), a survey was also undertaken to see further if a clear, constant association between a specific type of hand anomaly and a particular kind of congenital heart lesion could be demonstrated.

MATERIAL AND METHODS

Identification of Subjects: Because of the difficulty inherent in obtaining and examining a large sample size from a mobile population such as a clinic, it was decided to pursue these studies in a fixed population. Sonoma State Hospital, about one hour's drive north of San Francisco, serves the entire Northern California area of thirty-one counties in housing those mentally retarded adults and children who require state-supported hospitalization. Obviously, this is a very selected population with much inherent bias towards persons for which the fight for survival raises fundamental questions. Admission criteria include an I.Q. of less than 70, but in fact those children with higher I.Q. are sent to another state hospital with more specialized training programs. Thus, a recent article about Sonoma State Hospital stated that in a current population of 3359, 2435 are profoundly or severely retarded and 2070 had an I.Q. of less than 30 (Hobbs, 1967). Furthermore, admission to the hospital is partially based on the degree of social problem the child creates, e.g. attacking others, self-destructive, or incapable of ambulation or feeding or toilet training, and the ability of the home or community to cope with the situation. In addition, an obviously mentally retarded child with cardiac defects is rarely offered either palliative or corrective surgery. Thus those children with major anomalies associated with high early mortality often

never reach Sonoma to be included in this population.

Thus, the bias inherent in the population was well recognized, but this population was chosen as one relatively fixed in time and space which could be examined as a pilot study and from which any positive results derived could then be reinvestigated in a normal population. As the association of hand defects and cardiac anomalies in Down's syndrome is well known, these patients were excluded to avoid markedly prejudicing the data. All other patients in the hospital, regardless of cause of mental deficiency, and including all ages (from birth to eighty years) were studied.

Selection of Subjects: Two sample groups were chosen from the total patient population. The first group were those patients who had hand anomalies and the second was a control group of 10% random sample of patients without hand malformations. Both these same groups were then subjected to a specified evaluation of cardiac function.

Procedure for Making and Recording Observations: During summer, 1965, the entire hospital population of 3,439 patients was surveyed for hand malformations by the writer.

A list of patients was prepared prior to visiting each ward. The 392 patients with Down's syndrome were noted and excluded on a priori grounds, reducing the population to be surveyed to 3,047 patients with all types of mental deficiency other than Down's syndrome.

Furthermore, those patients who had been previously

diagnosed and noted in the master file as having hand defects were noted. Thus patients who had had anomalies such as rudimentary sixth digits which had been repaired before entering Sonoma were included in the group with hand malformations.

Each ward population was then surveyed by the writer for upper-extremity deformities. The patient was asked to extend his fingers and display alternately both the backs and palms of his hands to the examiner. In uncooperative subjects, the examiner opened the hand, insofar as possible. Each ward was visited on at least two different days to insure that the maximum number of patients would be seen. Of the 3,047 patients, 2,985 were actually visually inspected for hand deformities. Sixty-two patients were out of the hospital during the period of the ward survey, usually because they were spending the summer with their family at home.

Specific anomalies which could be easily discerned were ectrodactyly, polydactyly, and syndactyly. The standing height of the individual was considered in deciding which hands exhibited brachydactyly or arachnodactyly. Unequal length was defined as third and fourth digits equal in length or a second digit longer than the third. Incurved fifth fingers are those whose terminal phalanx curved toward the fourth finger; short fifth digits are those which terminated at less than or halfway between the first two flexion creases

of the fourth digit. Examples of these hand malformations follow (Table 1) on the next pages.

It was originally planned to x-ray the hands of all patients in the study and then quantify these visual observations of abnormality and normality by phalangeal/metacarpal and skeletal age/chronological age ratios. But it quickly became apparent that these mentally retarded patients were unable to cooperate in straightening their hands so that any measurements would be inaccurate and meaningless. Radiograms of the hands of the 216 patients with anomalies were, however, taken to document the malformations. As explained below, an additional patient with polydactyly was added to this group later.

Patients were assigned to categories of hand anomalies in the following order:

Order	Anomaly	Number with Anomaly	
1.	Ectrodactyly or	4	4
	Polydactyly	4	4
2.	Syndactyly	9	7
3.	unequal length	17	17
4.	Arachnodactyly or	88	75
	Brachydactyly	52	48
5.	Short and/or incurved fifth finger (s)	43	37
		217	192*

*These are the patients with hand anomalies on whom cardiac-evaluations were completed.

To select the control group without hand anomalies, a list of the total hospital population excluding those patients with Down's syndrome who were resident on June 6, 1966, was prepared (3,011 patients). Using a table of random numbers

Table I: Photographs and x-rays of hand anomalies observed in this study

The numbers are the patient numbers assigned to each subject. Complete information on each patient except for #0619, #0951, and #1171 can be found in Table III by comparing patient number.

Ectrodactyly # 2065

Left hand

← Thumbs →

Right hand

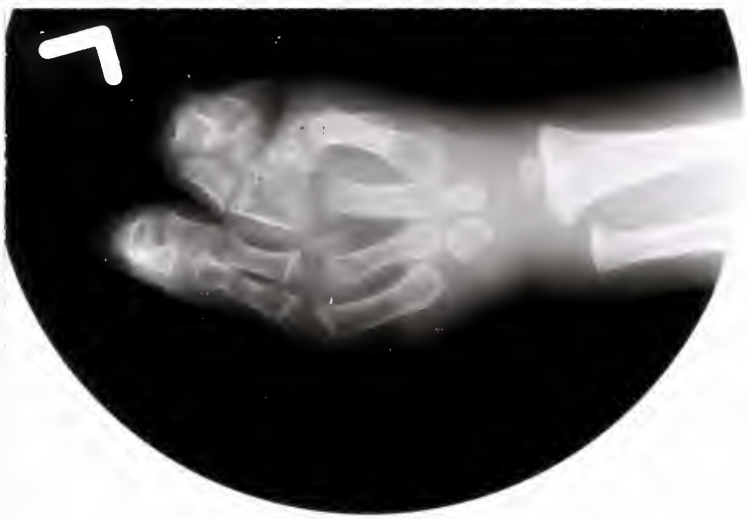
Syndactyly #1885

x-ray on next page

Syndactyly # 1885

Syndactyly
after operation

2101



Syndactyly
after operation

0956

Unequal length
(i.e. second finger
is longest)

#1662

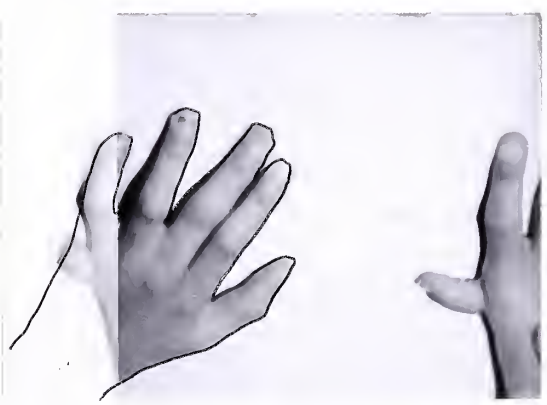
Arachnodactyly #0619

Arachnodactyly #1836

Brachy dactyly #0479

Possible Holt-Oram Syndrome #1775

Normal left hand



Normal left hand outlined with fingerlike right thumb superimposed

Fingerlike right thumb

X-ray on next page

Brachydactyly with
finger like right thumb

#1775

Short and
incurved
fifth fingers

0961

Shortened and incurved fifth fingers with only two phalanges

#1171

a control group of 10% was then chosen. Of the 301 patients thus identified, 18 were excluded because they had previously been determined to have hand anomalies. Another 31 patients were new to the hospital since the preceding year and thus had not been visually examined. However, on visual survey, only one of these was found to have a hand anomaly (polydactyly) and she was added to the group with hand anomalies. As the admission policy remained consistent, it is likely the 31 patients of the random sample new to the hospital over the preceding year did not differ substantially from the patients in residence in summer, 1965.

These two groups of subjects were then subject to a cardiac evaluation done by the consultant cardiologist and the writer. Workup included chart review and history, physical examination with primary emphasis on cardiovascular system, electrocardiogram, and posterior-anterior and left lateral chest x-rays. If congenital heart disease was suspected from these studies, x-rays of barium swallow with posterior-anterior, left lateral, and right and left oblique views were done and the patient was reexamined. When it was possible, cardiac catheterization was done to substantiate the diagnosis. Information which had been obtained at cardiac surgery was also used in establishing the diagnosis.

It was possible to complete the cardiac evaluations or obtain an autopsy report on 192 of 217 (88%) patients with hand anomalies and on 267 of 282 (95%) patients without hand

anomalies. The remainder of patients either were transferred to another institution before these studies could be completed or died without necropsy being performed. Thus this study is composed of information obtained on the hand and heart malformations of 459 of a possible 499 patients. Table II shows demographic information about the 459 patients in the study.

Table II

Characteristic		Hand anomaly patients N = 192	Normal hand patients N = 267
Sex:			
Races together	Males	103 = 53.6%	150 = 56.2%
	Females	89 = 46.4%	117 = 43.8%
Race: Sexes together	White	150 = 78.1%	147 = 92.5%
	Negro	30 = 15.6%	15 = 5.6%
	Other races	12 = 6.3%	5 = 1.9%
Diagnosis:	Diagnosis of mental retardation, with congenital cerebral defect of unknown cause	100 = 52.1%	128 = 47.9%

The percentage of males and females in the two groups appears to be approximately the same.

There is an obvious increase in the percentage of Negroes with hand anomalies as compared to a random sample of the population without hand malformations. One might expect that a large number of Negroes with polydactyly would explain this as polydactyly is known to be much more common in Negroes. However, of four patients with polydactyly, only one was a Negro. Thus, there seems to be no readily apparent

explanation for the increased numbers of Negroes with hand anomalies found in this population.

A striking fact was the lack of knowledge of the cause of mental retardation in the vast majority of these patients. More than half of the patients at Sonoma State Hospital are classified under a single "wastebasket" category,"mental retardation due to congenital cerebral defect of unknown cause."

RESULTS

The prevalence of hand anomalies detected on visual survey of the population of mentally retarded (excluding Down's syndrome patients) resident at Sonoma State Hospital during summer, 1965, was 7.3% (216/2985). In a 10% random sample of the population (excluding Down's syndrome patients) resident at Sonoma State Hospital on June 6, 1966, the prevalence of hand abnormalities was 6.3% (19/301).

The prevalence of congenital heart malformations estimated from a 10% random sample of the population (excluding Down's syndrome patients) resident at Sonoma State Hospital on June 6, 1966, was 3.2% (9/285).

Table III on the following page details specific information on the patients found to have congenital cardiac defects and the hand anomalies with which these were associated.

TABLE III

Hand Anomaly	Patient Number	Cardiac Diagnosis	Sex	Race	Year Birth	IQ
			Mental Retardation Diagnosis			
None	2389	Atrial and ventricular septal defects; pulmonary hypertension[1,2]	Female	White	1946	42
			Congenital encephalopathy with prenatal infection			
None	2323	Ventricular septal defect[1]	Female	White	1945	05
			M.R. of unknown cause			
None	0185	Endocardial cushion defect[1]	Male	White	1959	28
			M.R. of unknown cause			
None	0015	Anomaly of great vessels[1]	Female	White	1955	10
			M.R. of unknown cause			
None	2587	Anomaly of aortic arch[1]	Male	White	1960	15
			M.R. of unknown cause			
None	1832	Aberrant right subclavian vein; diverticulum of right ventricle; ? patent ductus arteriosus[1,2]	Male	White	1944	10
			M.R. of unknown cause			
None	1081	Pulmonic stenosis[1,4]	Male	White	1947	21
			M.R. of unknown cause			
None	1819	Pulmonic stenosis[1]	Male	Negro	1958	35
			M.R. due to maternal rubella			
Ectro-dactyly	2065	Right aberrant subclavian artery[1]	Male	White	1959	25
			M.R. of unknown cause; ?Cornelia deLange			

continued...../

Hand Anomaly	Patient Number	Cardiac Diagnosis	Sex	Race	Year Birth	IQ
			Mental Retardation Diagnosis			
Poly-dactyly	1413	Patent foramen ovale; ventricular septal defect[4]	Female	Chinese	1966	--
			M.R. with trisomy of Ch. 17--18			
Syn-dactyly	2101	Dextrorotation heart with other malformation [1]	Male	White	1965	50
			M.R.; Apert's syndrome			
Syn-dactyly	0956	Left persistent superior vena cava[1]	Female	White	1955	40
			M.R.; Apert's syndrome			
Syn-dactyly	1885	Circumflex aorta[1]	Female	White	1902	30
			M.R.: Apert's syndrome			
Unequal length	1662	Dextrocardia[1]	Female	White	1941	20
			M.R. of unknown cause			
Arachno-dactyly	1836	Patent ductus arteriosus[1,3]	Female	White	1949	20
			M.R. of unknown cause			
Arachno-dactyly	1747	Patent ductus arteriosus; diverticulum right ventricle[1,2,3]	Male	White	1952	10
			Congenital encephalopathy with prenatal infection			
Arachno-dactyly	2225	Aortic stenosis and incompetence[1]	Female	White	1953	10
			M.R. due to postnatal cerebral anoxia			
Arachno-dactyly	1287	Aortic incompetence[1,2]	Male	White	1937	31
			M.R.; Marfan's syndrome			
Arachno dactyly	0619	Aortic incompetence[1]	Female	Negro	1950	43
			M.R.; Marfan's syndrome			

continued...../

Hand Anomaly	Patient Number	Cardiac Diagnosis	Sex	Race	Year Birth	IQ
			Mental Retardation Diagnosis			
Brachy-dactyly	3012	Patent foramen ovale[4]	Male	White	1946	25
			M.R.; Morquio's disease			
Brachy-dactyly	1775	Atrial septal defect[1]	Female	White	1952	08
			M.R. of unknown cause			
Brachy-dactyly	1855	Atrial septal defect[1]	Female	White	1935	10
			M.R.; encephalopathy, postnatal cerebral infection			
Brachy-dactyly	0479	Atrial and ventricular septal defects,[1,2,3]	Female	White	1952	10
			M.R. of unknown cause			
Brachy-dactyly	3013	Atrial and ventricular septal defects; pulmonary hypertension[1,2]	Female	White	1937	27
			M.R.; environmental deprivation			
Short fifth	2360	Patent foramen ovale; partial anomalous return right atrium[1,2,4]	Female	White	1960	10
			M.R.; Cornelia de Lange syndrome			
Short fifth	2340	Anomalous great vessel; rehumatic heart disease with aortic stenosis[1]	Male	White	1937	52
			M.R.; cultural-familial			
Short fifth	0594	Pulmonic stenosis[1]	Male	White	1943	28
			M.R. of unknown cause; ?Cornelia de Lange syndrome			

1 - Cardiac evaluation including EKG and barium swallow x-rays
2 - Cardiac catheterization and/or angio cardiography
3 - Surgery
4 - Autopsy
M.R. = Mental Retardation

Of 192 patients with hand malformations, 19 were found also to have a congenital heart abnormality. Of 267 patients with normal hands, 8 had a congenital cardiac defect.

TABLE IV

	Patients with hand anomalies	Patients without hand anomalies	Totals
Patients with congenital heart lesions	19	8	27
Patients without congenital heart lesions	173	259	432
Totals	192	267	459

This data was analyzed by the chi-square method using Yates correction for continuity. Chi-square is then 8.41 with one degree of freedom, which is significant at the $p < 0.01$ level and shows that the association of hand anomalies and heart malformations is statistically significant as regards the null hypothesis.

Of those with hand abnormalities 9.9% also had a congenital heart lesion. Of those without hand malformations, only 3.0% also had a congenital cardiac defect. Thus those with hand anomalies had a statistically significant three-fold increase in congenital cardiac malformations.

DISCUSSION

Both upper extremity and congenital cardiac malformations were considerably more common in this mentally retarded, state-institutionalized population than in the general population. This suggests that the agent which produced mental retardation was often sufficiently damaging to produce other associated anomalies.

None of the cases of the Holt-Oram syndrome previously recorded in the literature (See Appendix I) had been described in mental defectives. Only one case which probably fits into the Holt-Oram pattern was found in this survey of an institution for the mentally handicapped (patient number 1775).

This patient was a fifteen-year-old white female who was felt on clinical examination (including radiological four-way view of the heart with contrast media) to have an atrial septal defect (permission for confirmatory cardiac catheterization was refused). Her electrocardiogram was abnormal with a P-R interval of 0.14 seconds, long for a rate of 120 beats/minute. It also showed right axis deviation and right ventricular hypertrophy. Roentgenogram of the upper extremities showed on the right hand a lack of the first metacarpal and two rudimentary phalanges on a fingerlike thumb. The right multangulum major and minor were fused and the navicular was either absent or fused with the multanguli. The other carpals were normal. The terminal phalanx of the left fifth finger was short and the tuft of the terminal phalanx of the fourth

finger was notched. Skeletal age was between 13 years and 13 years, 6 months, by the standards of Gruelich and Pyle (1959), for a chronological age of 14 years, 4 months.

The number of patients with both cardiovascular lesions and hand anomalies was too small to enable one to determine whether specific types of each malformation were associated. However, several interesting observations can be made from inspection of the table of hand and heart defects observed to be associated.

Atrial septal defect was associated only with brachydactyly. Of five patients with brachydactyly and congenital heart disease, two had atrial septal defect and two had atrial and ventricular septal defects. The fifth patient with brachydactyly was found at autopsy to have a patent foramen ovale.

Both of the patients with patent ductus arteriosus also had arachnodactyly. The other three patients with arachnodactyly also had aortic incompetence; two of these three had the typical anomalies of Marfan's syndrome.

None of the patients with hand malformations had transposition of the great vessels or persistent truncus arteriosus. However, both these lesions have a high early mortality and patients with these defects might not have lived long enough to be admitted to Sonoma State Hospital.

The most important finding of this study is that the incidence of congenital heart malformation was significantly

higher in those with hand anomalies than in a control group without hand anomalies. However, this is a pilot study and this finding should be reconfirmed in mentally normal children.

It would seem that the physician could indeed use the presence of an upper limb anomaly seen on physical examination to alert him to the increased probability of congenital heart disease. It would be important for him to follow and reevaluate the child so that defects discovered later can be either palliated or corrected before irreversible pulmonary hypertension has set in.

SUMMARY

This survey of the association of congenital hand and heart malformations was carried out in a California state hospital for the mentally retarded. As the association of hand and cardiac anomalies in Down's syndrome is well known, patients with this diagnosis were excluded to avoid prejudicing the data, but all other patients who were resident in the hospital while the study was done were included, regardless of diagnosis.

On visual inspection of 2985 patients 216 were found to have hand malformations, consisting of ectrodactyly, polydactyly, syndactyly, unequal length, arachnodactyly, brachydactyly, or short and/or incurved fifth finger. Cardiac evaluations were completed on 192 of these patients with hand anomalies of whom 19 were found to have congenital cardiac defects.

cardiac evaluation of a randomly chosen sample of 267 patients without hand anomalies, 8 had congenital heart abnormalities.

Thus, 459 mentally retarded, state institutionalized patients had evaluations for the presence of hand and heart anomalies. Those patients with hand malformations had a statistically significant threefold increase in the prevalence of congenital cardiac defect as compared to a randomly selected control group with normal hands. However, the numbers were not sufficiently large to enable one to correlate specific

kinds of congenital heart lesions.

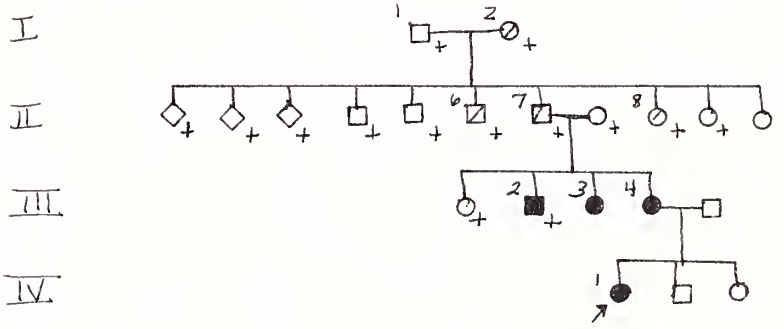
It would seem that the physician who finds on examination of the infant a hand abnormality should be alerted to follow the child for congenital heart disease.

Appendix I: Pedigrees of reported cases of the Holt-Oram syndrome with accompanying charts detailing the specific lesions observed.

Symbols used:

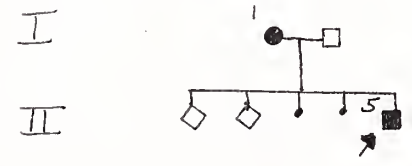
- Skeletal anomaly
- Cardiovascular anomaly
- Cardiovascular anomaly probable
- Skeletal anomaly probable
- Cardiovascular and skeletal anomalies probable

Holt and Oram, 1960

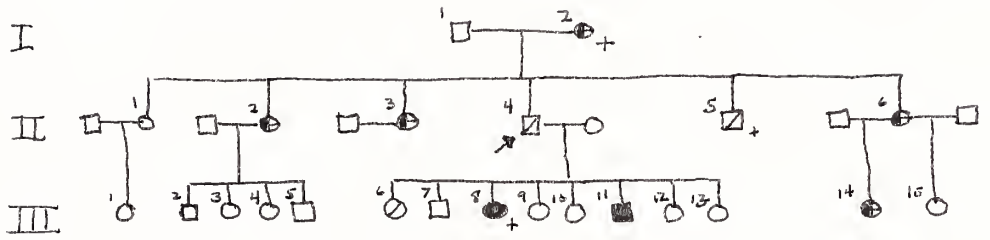


McKusick, 1961 and 1964

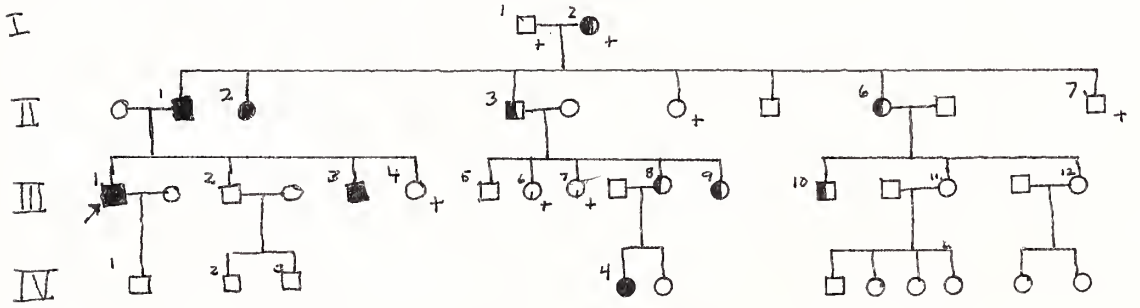
Zetterqvist, 1963



Kuhn, Schaaf, and Wagner, 1963

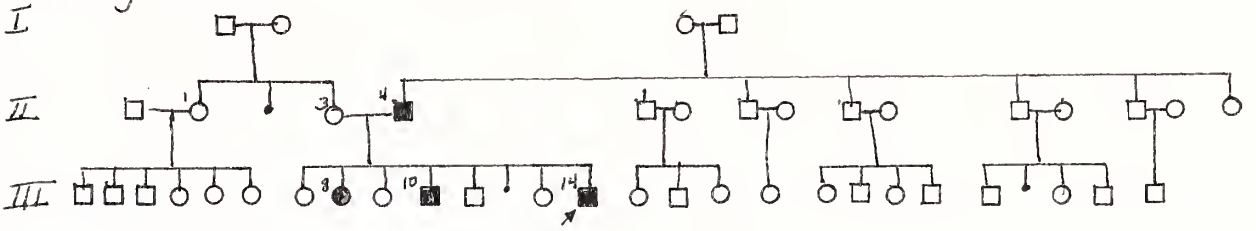


Pruzanski, 1964

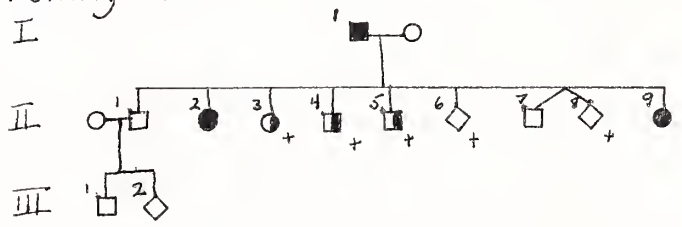


Holmes, 1965

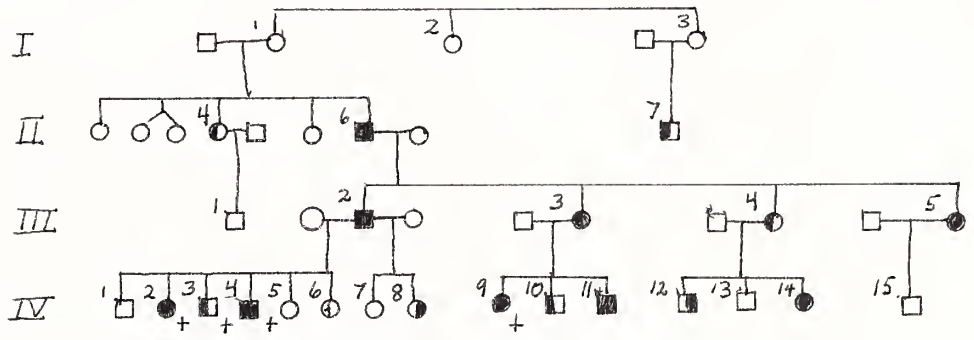
Family M



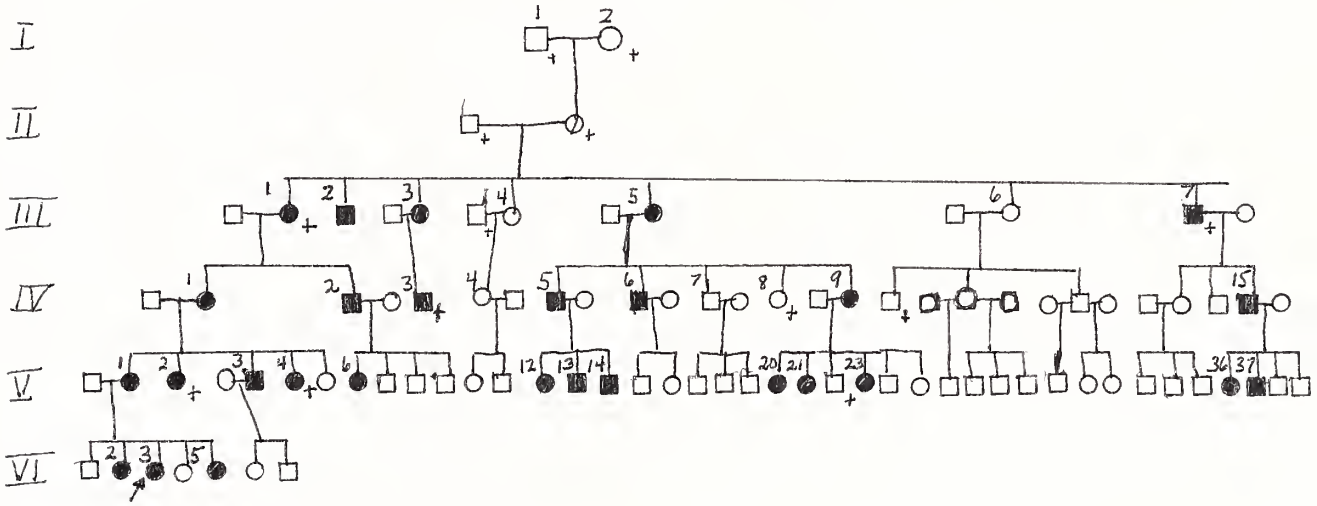
Family H



Lewis, Bruce, Baum, and Motulsky, 1965

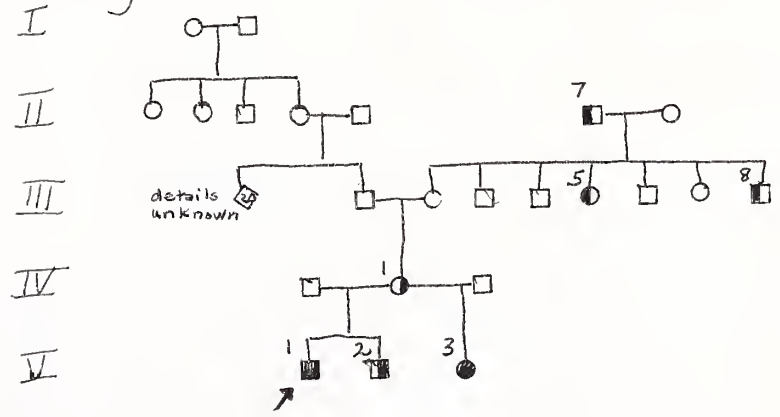


Gall, Stern, Cohen, Adams, and Davidson, 1966

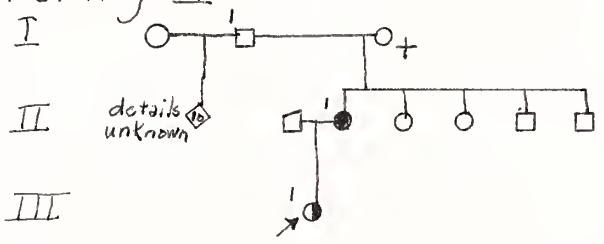


Massaumi, and Nutter, 1966

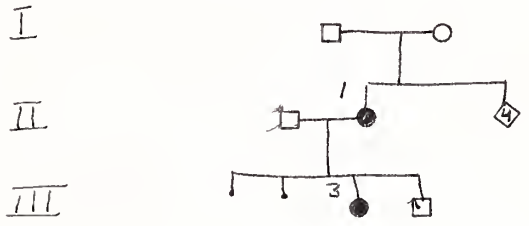
Family I



Family II



Ehlers and Engle, 1966



Cascos, 1967

Symbols used in charts following detailing the specific lesions observed

Captions
- R=Right
- L=Left
- C=Carpals
- MC=Metacarpals
- F=Forearm
- E=Elbow
- S=Shoulders
- S′=Sternum

Family member
- I-1=Number on pedigree chart

Age
- Age is in years.
- a.=alive
- d.=dead

Cardiac defects
- CHD=Congenital heart disease
- ASD=Atrial septal defect
- VSD=Ventricular septal defect
- PFO=Patent foramen ovale
- PDA=Patent ductus arteriosus
- PPH="Primary pulmonary hypertension"
- 1=Suspected
- 2=Clinical examination including cardiac x-rays with barium swallow
- 3=Cardiac catheterization and/or angiocardiography
- 4=Surgery
- 5=Autopsy

Cardiac catheterization
- R=Right
- L=Left

Electrocardiogram
- PVC=Premature ventricular contraction
- P-R=P-R interval measured in seconds
- A-V=Atrial-ventricular
- IRBBB=Incomplete right bundle branch block
- RBBB=Right bundle branch block
- RVH=Right ventricular hypertrophy
- LVH=Left ventricular hypertrophy
- RAD=Right axis deviation

Upper-extremity abnormalities
- F=Fingerlike
- 3=Three phalanges
- 2=Two phalanges
- A=Absent
- +=Abnormal

Study Family member; age	Cardiac defect	Cardiac catheterization	Electrocardiogram	Thumbs R	Thumbs L	Fingers	C MC	F E	S	S′	Karyotype
Holt and Oram, 1960											
I-2 Maternal great grandmother d.	CHD[1]										
II-6 Maternal great uncle d. 55	CHD[1]										
II-7 Maternal grandfather d. 65	CHD[1]										
II-8 Maternal great aunt d.	CHD[1]										
III-2 Maternal uncle d. 52	ASD[5]		Multiple PVC's RBBB; RVH	F3	A		+	+			
III-3 Maternal aunt a. 52	ASD[2]		Bradycardia with P-R 0.28; auricular fibrillation						+		

Study Family member; age	Cardiac defect	Cardiac catheterization	Electrocardiogram	Thumbs R	Thumbs L	Fingers	C MC	F E	S	S′	Karyotype
III-4 Mother a. 46	ASD[2]	Unsuccessful; hypoplastic veins	Sinus bradycardia with occasional interpolated ectopic beats and nodal escape; biventricular strain	F3	F3		+	+			
IV-1 Propositus, female a. 13	ASD[2]	Unsuccessful; hypoplastic veins	Sinus rhythm with P-R 0.22; RAD; wandering pacemaker and nodal escape	F3	F3		+	+			
McKusick, 1961 and 1964											
I-2 Mother	ASD[4]			F3	F3						
II-1 Propositus, female	ASD[3,4]			F3	A		+				
Zetterqvist, 1963											
I-1 Mother a. 64	ASD, secundum[4]	L→R shunt, 3/1	Sinus bradycardia with P-R 0.20-0.26; RBBB; RAD; ectopic supraventricular focus of IRBBB	A	F3						
II-5 Propositus, male a. 6	ASD, secundum[4]	L→R shunt, 2/1	Regular rhythm to ectopic auricular pacemaker; RAD	F2	F2		+				Normal male

Study Family member; age	Cardiac defect	Cardiac catheterization	Electrocardiogram	Thumbs R	Thumbs L	Fingers	C MC	F E	S	S′	Karyotype
Kuhn, Schaaf, and Wagner, 1963											
Heart lesion was felt to be "primary pulmonary hypertension" (PPH), but diagnostic studies were incomplete and inconclusive. Electrocardiogram showed right ventricular hypertrophy in all cases, with only one case of right bundle branch block (not specified which case).											
I-2 Mother d. 46 of "heart condition"	PPH[1]			F	A	+		+			
II-2 Sister	PPH[2]			F	F			+			
II-3 Sister a. 32	PPH[2]					+					
II-4 Proposita, male	Normal[3]	No shunt				+		+			
III-6 Daughter a. 15	PPH[1]			F	F			+			
III-8 Daughter d. 2 mo.	PFO; PDA; subaortic septal defect[5]				A			+	+		
III-11 Son d. 3 mo.	PFO[5]				F		+				
II-5 Brother d. 3 mo of "cardiac disease"	PPH[1]			Hand anomalies, not further specified							

Study Family member; age	Cardiac defect	Cardiac catheterization	Electrocardiogram	Thumbs R	Thumbs L	Fingers	C MC	F E	S	S′	Karyotype
II-6 Sister	PPH[1]				A	+	+	+	+	+	
III-14 Niece a. 10	PPH[2]			A	A	+	+	+	+	+	
Pruzanski, 1964											
I-2 Paternal grandmother d.				A	A			+			
II-1 Father a. 52	ASD, secundum[2]		P-R 0.24; IRBBB; RAD	A	A	+	+	+			
III-1 Propositus, male a. 28	ASD, secundum[3,4]	L→R 9.4 l.	P-R 0.24; biatrial hypertrophy; RVH; RAD	A				+			
IV-1 Son a. 1	Normal[2]			Normal							
III-3 Brother a. 14	ASD with another malformation[2]		P-R 0.28-0.30; RAD		F	+	+	+			
II-2 Paternal aunt a. 45	ASD, secundum[2]		P-R 0.36; IRBBB; biatrial hypertrophy; RVH; RAD	A	A	+	+	+			
II-3 Paternal uncle a. 32	CHD[2]		Normal	A	A	+	+	+			

Study Family member; age	Cardiac defect	Cardiac catheterization	Electrocardiogram	Thumbs R	Thumbs L	Fingers	C MC	F E	S	S′	Karyotype
III-8 Paternal cousin a. 32	?			A	A			+			
IV-4 Paternal cousin a. 9	ASD[2]			A	A	+		+			
III-9 Paternal cousin	?				A	+					
II-6 Paternal aunt a. 66	?			A	A	+		+			
III-10 Paternal cousin a. 30	Acyanotic CHD[2]			A	A	+					
Holmes, 1965 Family M											
II-4 Father a. 32	VSD[2]		Rate 68; sinus; P-R 0.24	A	F2		+	+		+	Normal male
III-8 Sister a. 7	PDA; VSD; Pulmonary coarctation of aorta[3]	hypertension	Rate 95; sinus; P-R 0.16; IRBBB; RVH; LVH	+	+	+	+			+	Normal female
III-10 Brother a. 4	VSD[2]		Normal; rate 100; P-R 0.16	A	F1		+	+		+	Normal male

Study Family member; age	Cardiac defect	Cardiac catheterization	Electrocardiogram	Thumbs R	Thumbs L	Fingers	C MC	F E	S	S′	Karyotype
III-14 Propositus, male a. 5 mo.	VSD[3]		Normal; rate 140; sinus; P-R 0.16	F2	F2		+				Normal male
Family H											
I-1 Father a.	ASD, secundum[2]		IRBBB	F3	F3					+	
II-2 Daughter a. 24	ASD, endo-cardial cushion defect	Pulmonary hypertension		F3	A		+				
II-3 Daughter d. infancy	CHD[1]										
II-4 Son d. infancy	CHD[1]										
II-5 Son d. infancy	CHD[1]										
II-9 Daughter a. 8	VSD[3]	Pulmonary hypertension		F3	A	+	+	+			

Study Family member; age	Cardiac defect	Cardiac catheterization	Electrocardiogram	Thumbs R	Thumbs L	Fingers	C MC	F E	S	S′	Karyotype
Lewis, Bruce, Baum, and Motulsky, 1965											
II-4 Paternal grandaunt a.	?							+			
II-7 Paternal granduncle	?			+	+						
II-6 Grandfather a. 63	Retroesophageal right subclavian artery[2]		Sinus; first degree A-V block; RBBB	F	F		+	+			Normal male
III-2 Father a. 32	ASD, secundum[3,4]		RBBB; RAD	F	A		+	+		+	
IV-2 Daughter d. 2	VSD; anomalous right subclavian artery from descending aorta[2]		RVH; RAD	A	A	+	+	+	+	+	
IV-3 Son d. 3 mo.	Normal[5]			A	A						
IV-4 Son d. 3 mo.	VSD[3,5]			A	A	+	+	+	+	+	
IV-6 Daughter a. 3 mo.	Normal[2]									+	
IV-8 Daughter a. 9	Anomalous right subclavian artery[3]	Pulmonary hypertension	First degree A-V block; RVH; right heart strain								

Study Family member; age	Cardiac defect	Cardiac catheterization	Electrocardiogram	Thumbs R	Thumbs L	Fingers	C MC	F E	S	S′	Karyotype
III-3 Mother d. 24	ASD[3]					+		+			
IV-9 Daughter d. 3 mo.	VSD[5]			F							
IV-10 Son a. 12	Normal[2]		Wandering pacemaker	A	A			+	+		
IV-11 Son d. 3 mo.	Transposition of great vessels[2]		First degree A-V block; interventricular conduction defect	F	F	+	+	+			
III-4 Mother a. 25	Normal[3]	Normal	Normal except widened QRS		F		+	+		+	
IV-12 Son a. 6	ASD[3,4]		IRBBB								
IV-14 Daughter a. 3	ASD, VSD[3]	Pulmonary hypertension	RVH	F	F	+					
III-5 Mother a. 22	Entire coronary circulation from single common trunk originating from right coronary ostium[3]	Normal	LVH	F	A		+	+	+		
IV-15 Son aborted at 20 wks. gestation	ASD[5]										

Study Family member; age	Cardiac defect	Cardiac catheterization	Electrocardiogram	Thumbs R	Thumbs L	Fingers	C MC	F E	S	S′	Karyotypes
Gall, Stern, Cohen, Adams, and Davidson, 1966											
Of seven persons affected and one person unaffected, all had normal karyotypes.				All had some malformation and/or hypoplasia of upper extremity and shoulder girdle, with left side more severely affected.							
V-1 Mother	ASD[3]										
VI-2 Sister	VSD; PDA; Pulmonary anomalous left coronary artery[3]	Pulmonary hypertension	Normal								
VI-3 Proposita, female	Abnormally heavily trabeculated right ventricle[3]										
VI-5 Sister a. 10	VSD; PDA; Pulmonary left superior vena cava emptying anomalously into right atrium[3,4]	Pulmonary hypertension		F	F						
Distant cousins of proposita:											
IV-5 Father	ASD; VSD[3]										
V-12 Daughter	Persistent left superior vena cava; abnormally heavily trabeculated right ventricle[3]										
V-13 Son a. 15	VSD[3]		Occasional extrasystole; variable P-R	F	F			+		+	

Study Family member; age	Cardiac defect	Cardiac catheterization	Electrocardiogram	Thumbs R	Thumbs L	Fingers	C MC	F E	S	S′	Karyotype
V-14 Son	VSD[3]			F	F			+	+		
IV-6 Father	VSD; persistent left superior vena cava[3]	Pulmonary hypertension									
IV-9 Mother	Abnormally heavily trabeculated right ventricle[3]										
V-20 Daughter	VSD[3]										
V-21 Daughter	ASD; VSD[2]										
V-23 Daughter	ASD; VSD[2]										
IV-15 Father	ASD[3]										
Massaumi and Nutter, 1966											
Family I											
II-7 Maternal greatgrandfather	?				A		+	+			
III-5 Maternal greataunt	?				A		+	+			
III-8 Maternal greatuncle	?				A		+	+			
IV-1 Mother a. 47	ASD, secundum[3]	L→R shunt; mild pulmonary hypertension	Arrhythmia; RBBB								Normal female

Study Family member; age	Cardiac defect	Cardiac catheterization	Electrocardiogram	Thumbs R	Thumbs L	Fingers	C MC	F E	S	S	Karyotype
V-1 Propositus, male a. 19	ASD, secundum[3]		First degree A-V block; IRBBB	F3	A		+	+			No. 16 variant
V-2 Brother	Normal		Wolff-Parkinson-White	F3							
V-3 Half-sister a. 38	ASD, secundum[3]		Arrhythmia; RBBB	+	+	+					
Family II											
II-1 Mother a. 23	ASD, secundum[3,4]	L→R shunt, 2/1	RBBB	F3	A		+	+			No. 16 variant
III-1 Propositus, female a. 2	ASD, secundum; moderate valvular pulmonary stenosis; peripheral pulmonary stenosis[3]	L→R shunt, 3.8/1	RVH								Normal female
Ehlers and Engle, 1966											
II-1 Propositus, female	ASD, secundum[3,4]			F	A	+	+	+	+		Normal female
III-3 Daughter	ASD, secundum[3,4]			F2	F2	+	+	+	+		Normal female

Study Family member; age	Cardiac defect	Cardiac catheterization	Electrocardiogram	Thumbs R	Thumbs L	Fingers	C MC	F E	S	S´	Karyotype
Cascos, 1967											
I-1 Mother a. 32	Normal[2]		P-R 0.22	F3	F2	+	+				
II-1 Daughter a. 9	ASD, secundum[4]		Sinus bradycardia to nodal syncope; IRBBB; RAD								
II-2 Son a. 8	ASD, secundum[4]		Atrial flutter; 2:1 to 3:1 A-V conduction								
II-3 Daughter a. 3	ASD, secundum[2]		Sinus bradycardia to nodal escape; IRBBB	F3	A	+	+				Normal female

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